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# Exploring the Role of Rheumatic and Musculoskeletal Diseases in Multimorbidity

*Daniela Simões and Raquel Lucas*

## Abstract

Non-communicable diseases (NCDs) frequently aggregate due to shared pathophysiological mechanisms, either as sequential steps in the same causal pathway or as common results of the same exposures, leading to a high prevalence of disease co-occurrence, a phenomenon known as multimorbidity. Multimorbidity is a patient-centered concept where all morbidities are regarded of equal importance irrespective of whether they started before or after any other disease in question. Rheumatic and musculoskeletal diseases (RMDs) are among the most prevalent groups of NCDs, and probably due to their high incidence and low case fatality, they are highly susceptible to multimorbidity. Complex patients, such as some of those with multimorbidity, are nowadays the norm, implying a growing concern that clinical practice guidelines fail to adequately address the care of complex patients. The ramifications of suffering from multimorbidity unfold for each patient, within their social, educational, cultural, behavioral, economic, and environmental contexts, which in turn affect disease management.

**Keywords:** rheumatic and musculoskeletal diseases, non-communicable diseases, multimorbidity, patient-centered care

## 1. Introduction

Multimorbidity is the concurrent presence of more than one chronic disease [1] in the same person and affects a substantial part of the adult population. Although the medical education and medical research are focused mainly on individual diseases, the study of multimorbidity is increasingly common. A recent bibliometric study revealed that the number of publications regarding this topic increased 60% after 2010 [2]. Nevertheless, the study of multimorbidity is still not sufficient to reduce the gap between the available evidence for single condition vs. multiple conditions [2].

Multimorbidity is a relatively new concept and a challenging area in clinical practice globally, and some confusion persists regarding its definition. For instance, the terminologies multimorbidity and comorbidity have been used interchangeably despite their differences. Comorbidity, as originally described by Feinstein in 1970 [3], is used to describe any clinical entity coexisting with an index disease under study. This term and its definition are widely accepted and used. However, the definition of multimorbidity, which is the term most frequently used when no index disease is designated, is still not consensual. Indeed, only in 2018, the term

multimorbidity was accepted as a Medical Subject Heading (MeSH) by the United States National Library of Medicine and with the simple definition “the complex interactions of several co-existing diseases”. Despite this somehow insufficient definition, it is usually accepted that multimorbidity takes into account chronic or long-term diseases or conditions, including both physical and mental diseases, with none considered the index disease [4].

Despite the stated differences, the concepts of comorbidity and multimorbidity are not mutually exclusive or contradictory, but consider a patient with more than one disease at the same time from different perspectives. While comorbidity considers any additional disease as consequence, complication, or coincidence, multimorbidity is a more generic, patient-centered concept, where all morbidities are regarded of equal importance irrespective of whether they started before or after any other disease in question, and that contemplates all aspects of a patient's condition, including potential disease interactions and potential pathophysiological links [5]. Multimorbidity considers that the pathophysiological links between these diseases, syndromes, or conditions may overlap and that their management may interact to varying degrees.

Highly prevalent chronic diseases, such as arthritis, diabetes, chronic lower respiratory tract disease, or stroke, are known to co-occur frequently [6], and even less prevalent conditions still may occur in the same person at the same time. It is clear that, at the population level, diseases may aggregate due to chance alone, i.e., the more frequent a disease is, the more likely it is to coexist with others even in the absence of a direct causal relation, particularly for conditions which become more common with increasing age. However, non-communicable diseases (NCDs) also frequently aggregate due to shared pathophysiological mechanisms, either as sequential steps in the same causal pathway (causal multimorbidity) or as common results of the same exposures (associative multimorbidity) [7]. One example is a known causal pathway between rheumatoid arthritis and cardiovascular disease [8]. Another example is the increased risk of both osteoarthritis and type 2 diabetes in people with obesity, a shared risk factor between several NCDs that consequently increases the likelihood of these diseases clustering in the same subject [9]. This framework provides a causal or associative meaning to several mechanisms commonly used to explain for disease co-occurrence: general disease susceptibility, interaction between gene and environment, association between morbidities in a mutually reinforcing causal loop, effects on different organs of psychosocial and cultural factors, life events and coping styles, and common underlying pathogenic mechanisms, such as chronic inflammation [7, 10].

## **2. Multimorbidity burden**

Multimorbidity is becoming increasingly important in research and daily clinical practice. Its burden to both the individual and society is increasing, probably due to higher life expectancy, lowered thresholds for diagnoses, advances in medical care, and possibly due to a true increase in the prevalence of some chronic diseases [11]. Despite the existence of abundant information regarding epidemiology, risk factors, and management of individual chronic diseases, for multimorbidity only a few clinical guidelines exist making informed decisions harder. For example, following clinical practice guidelines for individual chronic conditions, a recent systematic review reported that a hypothetical 78-year-old woman with five chronic conditions [osteoporosis, osteoarthritis, diabetes type 2, hypertension, and chronic obstructive pulmonary disease (COPD)] would be prescribed up to 12 separate medications, taken at five times during the day, and should be engaged in

14 non-pharmacological activities [12, 13]. Given that each one of these diseases has different therapies, the management strategy for the patient with multimorbidity may be influenced by the care provided to each one of the conditions, including limitations of life expectancy, interactions between therapies, and/or contraindications to therapy for one condition due to other conditions [14]. Additionally, most times, the use of many services to manage individual diseases can become duplicative and inefficient and may be burdensome and unsafe for patients because of poor coordination and integration. In fact, a key aspect of multimorbidity is that chronic diseases are likely to act synergistically [15], causing an overall burden that can be larger than the sum of their individual impacts.

At the patient level, multimorbidity is associated with higher mortality [16], worsened functional status, and poorer quality of life [17]. Additionally, people living with multimorbidity have greater self-care needs [18] and are especially likely to rely on a caregiver for health management [19]. At the healthcare level, it implies increased risk of receiving less than best practice care [20], more frequent postoperative complications [21], longer hospitalization, higher likelihood of readmission [22], more frequent healthcare utilization, higher direct costs [23, 24], and increased use of polypharmacy with the potential for adverse drug effects [25]. With all these adverse health outcomes, the ramifications of suffering from multimorbidity affect the individual within social, educational, cultural, behavioral, economic, and environmental circumstances, which in turn affect disease management.

Studies have shown that age, household income, and family structure are the most important measured predictors of the multimorbidity status [26]. Moreover, multimorbidity tends to be more common in females than in males [26, 27]. The presence of multimorbidity also suggests higher risk of additional conditions, i.e., people with multimorbidity are at a higher risk of being diagnosed with two or more new diseases than those with no disease [28], probably due to increased interaction with healthcare professionals and higher healthcare utilization. Additionally, several important modifiable risk factors that are associated with the development of individual chronic diseases may play an important role in multimorbidity. These include lifestyle factors such as tobacco smoking and alcohol intake, over- and undernutrition, physical inactivity, and occupational exposures [29–32]. Many of these factors are common to multiple diseases. For instance, smoking increases the risk of chronic respiratory diseases, cardiovascular diseases, and neoplasms, while obesity increases the risk of cardiovascular diseases and musculoskeletal disorders. Therefore, it is not surprising that the presence of these risk factors increases the risk of a particular combination of chronic diseases. A recent bibliometric study showed that the risk factors most commonly mentioned in multimorbidity studies are physical activity and obesity/high body mass index [2]. Additionally, a recent overview of systematic reviews summarized the evidence on risk factors for multimorbidity into four groups: biomedical and individual factors (aging, women, high number of previous diseases, negative life events, external health locus of control, and mental disorders), health behaviors (smoking, overweight, obesity, high waist to hip ratio, and low physical activity), socioeconomic characteristics (lower social economic status, lower education, less social networks, full dependency, and unemployment), and social and environmental factors (living in urban areas in lower middle income country) [33].

Despite the increase in research outputs regarding multimorbidity, the evaluation of the burden of multimorbidity and its population impact remains challenging. In the European Union, there are an estimated 50 million people with multimorbidity, and this number is expected to grow as the population ages [34]. Estimates of the prevalence of multimorbidity vary from 4.4% to over 90% [35–37],



a discrepancy driven by distinct study populations or data sources, usually involving differences in demographic characteristics and disease types or classification. Despite this, up to the present, no gold standard exists regarding how to assess multimorbidity, and there is no consensus on which conditions should be considered or on the method used for measuring multimorbidity, which makes comparisons among studies difficult.

### **3. The role of rheumatic and musculoskeletal diseases in multimorbidity**

Rheumatic and musculoskeletal diseases (RMDs) are among the most prevalent groups of NCDs [38]. They are strong determinants of pain [39] and disability [40] and the first to third largest contributors to years lived with disability (YLDs) in almost all world regions [41]. Additionally, they have a high impact on quality of life [42], complexity of medication regimens [43], and affect the ability to continue paid employment [44]. Due to their high incidence and low case fatality, RMDs frequently co-exist with other conditions [37, 45]. Despite their well-known association with a wide scope of adverse health outcomes [46–49], the inclusion of RMDs in multimorbidity research tends to be inconsistent and selective. However, evidence supports that RMDs appear to form a principal component of certain multimorbidity clusters [50] and are common in multimorbidity [51, 52], with one study reporting that even after adjustment for age and gender, the odds of multimorbidity were greater in respondents with musculoskeletal conditions than those with any of the non-musculoskeletal conditions included in different definitions of multimorbidity assessed [51].

RMDs are also a highly heterogeneous group of NCDs [38], from inflammatory rheumatic diseases (such as rheumatoid arthritis and spondyloarthritis) to degenerative conditions (such as osteoarthritis), fragility conditions (such as osteoporosis), or regional pain syndromes (such as low back pain, neck pain and, the chronic widespread pain syndrome) [53]. RMDs are common throughout the life course, but some become even more common at older ages, in particular osteoarthritis. Despite this, RMDs are not always assessed in multimorbidity studies, and when assessed, they are usually restricted to osteoarthritis [54] or to broadly encapsulating categories that include arthritis, other joint disorders, or other painful conditions in the same category [26, 55].

It is plausible that the prevalence of multimorbidity might vary for subtypes of RMDs included in each definition. The subgroups with the highest prevalence of multimorbidity are typically osteoporosis, osteoarthritis, and inflammatory arthritis [51], but it remains to be determined whether RMDs in general, or only particular subgroups of RMDs, are associated with increased prevalence of multimorbidity.

Furthermore, multimorbidity research typically focuses on older people, naturally excluding generally less disabling RMDs, such as work-related musculoskeletal conditions. However, multimorbidity is not simply a process of aging [36], suggesting that to fully capture the burden of RMDs in multimorbidity a broader age range should be evaluated. As a matter of fact, considering that the presence of one condition increases the risk of multimorbidity in disease-specific populations (probably due to shared lifestyle and biomedical disease risk factors, as well as medication use [56] or iatrogenic effects [57]), the study of the role of RMDs in multimorbidity should start at young ages to fully capture the heterogeneity of RMDs, including soft tissue disorders or others that start at younger working ages.

Many important risk factors for common RMDs show remarkable overlap with risk factors for multimorbidity. For example, age and female gender are two of the most important non-modifiable risk factors for some RMDs [58], and as previously

stated, they are also common risk factors for multimorbidity. Modifiable risk factors such as obesity or low physical activity are importantly associated with osteoarthritis and regional pain syndromes, including low back pain [59]. Additionally, smoking is the main modifiable risk factor for inflammatory arthritis, and smoking, poor nutrition, and low physical activity are lifestyle risk factors for osteoporosis [60]. All these risk factors have been linked to multimorbidity in recent publications [29–32].

Because of the heterogeneous multimorbidity definitions used in different studies, it is difficult to fully assess the impact of RMDs on multimorbidity. However, RMDs usually aggregate with a wide set of NCDs. An Australian systematic review of population-based studies in the elderly found that over 50% of elderly patients with arthritis also had hypertension followed by cardiovascular diseases, dyslipidemia, diabetes, and mental health problems, whereas 60% of elderly patients with asthma reported arthritis followed by cardiovascular diseases and diabetes [61]. According to several systematic reviews, arthritis or osteoarthritis is usually comorbid with hypertension, cardiovascular diseases, dyslipidemia, diabetes, mental health problems, asthma, depression, and metabolic conditions [45, 61–63].

As previously described [64–66], RMDs frequently cluster with cardiometabolic conditions due to common pathophysiological risk factors, such as immobility, obesity, and systemic inflammation [67]. Additionally, pleuropulmonary disease may occur in patients with systemic autoimmune rheumatic diseases due to several causes, including infection in the treated patient, toxic medication reactions, and inherent manifestations of the diseases themselves [68]. Also, studies have shown a slightly increased risk of specific malignancies in people with rheumatoid arthritis [69], possibly due to smoking as a common risk factor for rheumatoid arthritis and lung cancer [70] and estrogen changes, which are common to rheumatoid arthritis and breast cancer [71]. A strong bidirectional relation between depressive states and musculoskeletal symptoms, especially pain, is well documented, which accounts for the clustering of these conditions [72]. These findings can be interpreted in the light of the current discussion about inflammatory as well as oxidative and nitrosative stress pathways that underpin the common pathophysiology of depression and RMDs [73]. Additionally, inflammatory cytokines, glucocorticoid treatment, immobilization, and reduced physical activity due to tender joints and muscle weakness have shown to play a key role in favoring low bone mineral density in RMDs [74], especially in people with rheumatoid arthritis [75].

The specific combination of RMDs with other NCDs also seems to have a strongly deleterious effect in adverse health outcomes. For example, co-occurrence of pulmonary and cardiac diseases is most often associated with mortality, but work disability is more strongly associated with depression [76]. Therefore, when trying to assess how multimorbidity affects prognosis, we need to define which disease combinations we are referring to and which outcome is of greatest interest. Slater and colleagues [77] found that among people with diabetes, cardiovascular, and respiratory diseases, comorbid musculoskeletal conditions increased the risk and accounted for a substantial proportion of activity limitations. Also, patients with rheumatoid arthritis and comorbidities are less likely to achieve treatment targets such as remission or low disease activity [78]. Others demonstrated that multimorbidity and depressive symptoms are strongly linked to functional limitations and lower self-rated health [79], that RMDs in multimorbidity worsen daily functioning and quality of life [17], and that multimorbidity is associated with frequent health-care utilization and higher costs for the healthcare system [80]. Depression seems to interact synergistically with arthritis and neck/back disorders to increase the odds of reporting chronic pain beyond an additive model [81]. Additionally, the presence of RMDs in the context of multimorbidity tends to amplify the risk of adverse work outcomes and especially of sick leave [52].

#### **4. The challenges of multimorbidity management**

The management of patients with multimorbidity is challenging. Although it could be expected that people with multimorbidity might be receiving better quality of healthcare than that individuals with only one disorder, at least partly because of greater contact with healthcare services [82], people with multimorbidity have more difficulties with disintegration of care, polypharmacy, and medical error because much specialized care is focused on the treatment of one disease [5]. Those with multimorbidity frequently receive care from family physicians, other medical specialists, and other healthcare professionals, such as nurses or physiotherapists, who may not be communicating effectively with each other [83]. Additionally, and despite the confirmed effectiveness of many individual treatments commonly used in chronic conditions, each additional therapy carries an additional burden, known as treatment burden, which includes physical effects of treatment, financial losses, and the psychosocial effects of time demands and dependence on others for assistance [84]. This means that people often suffer from a combination of disease and treatment burdens and that people receiving multiple treatments will have a higher treatment burden than those receiving only one treatment.

Currently, the main challenge of health professionals when targeting multimorbidity is to try to step aside from a disease-centered perspective, very deeply rooted in health professionals' education and strongly encouraged through pay-for-performance systems, to switch to the patient as the focus of treatment. For example, the typical treatment perspective for a patient with RMDs and other conditions focuses on the comorbidity concept, i.e., in the treatment of the index disease [5]. A medical doctor, usually a rheumatologist, will apply the treat-to-target concept to induce remission of that disease [85], hoping that this treatment will also positively affect non-RMD comorbidities. The treat-to-target approach is generally defined as a proactive treatment strategy, operationalized as a precise treatment algorithm, in which the clinician treats the patient aggressively enough to reach and maintain specific goals, such as remission or low disease activity [85]. In contrast, when considering the multimorbidity concept, the focus is on treating the patient, usually trying to improve overall well-being. In multimorbidity, it is harder to assess treatment effectiveness, and other concepts such as quality of life, overall function or health, and the patients' preferences should be also considered [5]. In order to help the clinicians, a recent clinical guideline suggesting a patient-centered approach to multimorbidity was published [86, 87]. It is important to notice that it is very difficult to publish guidelines concerning a disease-centered treatment for every combination of chronic conditions, which is one of the reasons why multimorbidity guidelines are more likely to take a patient-centered approach, targeting general well-being, quality of life, independence, autonomy, and improved function, but especially patient's goals, values, and priorities [86]. By implementing the concept of patient-centered care in daily practice, a greater effectiveness of diagnosis and treatment approaches and also improved clinical outcomes are expected.

This new clinical guideline suggests that in patient-centered care it is important to understand the patient's life, establishing what is important to them, and acknowledge the current disease and treatment burdens. After that, a revision of the patient's current medicines and other treatments should be done. The risks and benefits of each treatment (including non-pharmacological ones) should be weighted, and later, an individualized management plan, including timing of follow-up, should be developed and agreed upon with the patient [86]. Health professionals will have the most difficult task: to balance medical knowledge and expertise with patients' goals, when trying to reduce the impact of any conditions



on the adverse health outcomes that really worry the patient. It is not only about attaining one disease remission but rather to achieve a “healthy” life, and this is even more important when the patient is chronically ill.

Patient-centered care for patients with multimorbidity can be described as a care which (1) is attentive to patient’s psychosocial as well as physical needs, (2) explores the patient’s concerns and priorities for care, (3) conveys a sense of partnership between the patient and physician, (4) facilitates active patient involvement in decision-making, and (5) is coordinated across professionals, facilities, and support systems [88, 89]. However, the evidence regarding the effectiveness of such care is still lacking. The need for such evidence, including the need for patient care guidelines and health programs that are multiple disease-centered, is nowadays well established. Despite the recent publication of new guidelines and frameworks regarding patient-centered and integrated care [90, 91], the implementation of these recommendations in day-to-day work will require a re-organization in the way care is delivered. In a qualitative study, Bayliss and colleagues [18] explored the healthcare priorities of patients with multimorbidity. The priorities for patients were easy access to care and clinicians, but especially they desired healthcare providers who had a caring attitude and listened to them, understanding that their needs were unique and fluctuating. A recent systematic review [92] described comprehensive care programs targeting multimorbidity patients and estimated their effectiveness regarding improvement of patient- and caregiver-related outcomes, healthcare utilization, and costs. The authors concluded that providing comprehensive care might result in higher patient satisfaction, less depressive symptoms, a better health-related quality of life, or functioning, but also found that the evidence is still insufficient. More (good quality) studies using more appropriate outcome measures are needed [92].

Patient-centered care must be provided by a multidisciplinary team, and this is a great challenge. There must be clarity about who will be responsible for carrying out the different actions outlined in a plan, with appropriate support and coordination between professionals. Although it would be expected that several health professionals would have expertise in assessment and management of RMDs and differ mainly by the types of interventions they use, this is often not the case, given that different professionals have different curricula and often different perspectives regarding diseases and treatment goals [93]. So, it should be recognized that an integrated approach with all the disciplines and professionals working together is the ideal way of achieving the best outcome for the patient. Healthcare services should be aware of this paradigm shift and must provide integrated coordinated multidisciplinary care; however, this is a multifaceted challenge that cannot be overcome with a single effort.

## 5. Conclusion

Complex patients, such as some of those with multimorbidity, are nowadays the norm, implying a growing concern that clinical practice guidelines fail to adequately address the care of complex patients. As already mentioned, the ramifications of suffering from multimorbidity unfold for each patient, within their social, educational, cultural, behavioral, economic, and environmental contexts, which in turn affect disease management. The healthcare system in several countries is typically guided by clinical practice guidelines that are oriented toward single disease [94]. This poses a challenge for primary care professionals who try to implement evidence from these guidelines in patients with multimorbidity. As



described by Duffield and colleagues [53], people with multimorbidity are often required to carry out numerous tasks to maintain their health. The responsibilities listed by the authors include managing different tablets to be taken at specific times of day, week, or only occasionally; keeping stock of their pills, creams, inhalers, and injections; requesting repeat prescriptions on time; visiting the pharmacy to collect items; performing non-pharmacological treatments such as physiotherapy or other complementary interventions; and monitoring treatment effectiveness with regular lab analyses, physical tests, and medical appointments [53]. The time and effort required to remember and attend these appointments, including travel time, may require an additional treatment burden placed upon the individual [84]. Having a RMD as part of multimorbidity makes all of these activities even more difficult. People with arthritis report great difficulty or inability to grasp small objects; reach above one's head; sit more than 2 hours; lift or carry 10 pounds; climb a flight of stairs; push a heavy object; walk a 1/4 mile; stand for more than 2 hours; and stoop, bend, or kneel [95]. As a result of restricted mobility and function, having a RMD can hamper the execution of many of the tasks required in multimorbidity care, limiting people's ability to manage their health.

The impact of RMDs on patients and society should be acknowledged, as they are mostly non-fatal conditions with great effects at older ages. Regardless of the multimorbidity definition applied, musculoskeletal conditions are a common component of multimorbidity [51], and most working-age adults who met the definition of multimorbidity had a musculoskeletal condition [96]. This is an important finding because the strategies to include and classify musculoskeletal conditions within multimorbidity research have been inconsistent. Policy makers and public health teams should be aware of the importance of musculoskeletal health. Frequently, osteoarthritis and osteoporosis are seen as a natural consequence of aging and back pain as normal in working ages. The importance of early appropriate treatment for many musculoskeletal conditions in order to prevent chronicity and to reduce disability is undervalued. Often, adherence to treatment plans is less than optimal since patients are typically given little information about their condition; and many have misconceptions about treatments [97]. However, it is important to understand that even if the condition itself cannot be suppressed, health professionals can contribute to improve the patient's general well-being, quality of life, independence, autonomy, and general function.

Governments and public health teams along with healthcare stakeholders should take multimorbidity into account when designing, implementing, and evaluating public health education, programmes, and campaigns. They should identify and understand the needs and requirements of people living with multimorbidity (and with RMDs in particular) in their populations. They should also identify, prioritize, and target adverse health outcomes. They should acknowledge that targeting risk factors can potentially reduce the burden of multimorbidity in the long term. It is time to face multimorbidity.

In conclusion, although population aging has been a remarkable achievement of public health and clinical medicine, it poses great challenges that can only be overcome if clinicians, researchers, and policy makers are aware of the complexity of multimorbidity, which needs specialization, but also a holistic approach to ensure that patients receive coordinated care. However, more studies on RMDs and multimorbidity are still needed. Further evidence may help to better understand reasons for poorer health in certain groups and to aid their disease management. It may also contribute to assess the effect of multimorbidity on long-term outcomes, to identify prognostic factors, to develop effective interventions, and to support integrated patient-centered care programmes.

## Conflict of interest

All authors have declared that no conflict of interest exists.

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